



<b>IN THE UNITED STATES PATENT AND TRADEMARK OFFICE</b>	<i>Application Number</i>	09/910,082
	<i>Filing Date</i>	23 July 2001
	<i>First Named Inventor</i>	Baldomero M. OLIVERA
	<i>Group Art Unit</i>	1653
	<i>Examiner Name</i>	G.E. Bugaisky
	<i>Attorney Docket Number</i>	2314-241
<i>Title of the Invention:</i> <b>OMEGA-CONOPEPTIDES</b>		

Handwritten notes: "Election 4/9/03" and "11" with a checkmark.

### RESPONSE TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

In the Office Action mailed 3 December 2002, the Examiner restricted the claims into two Groups. Applicants provisionally elect Group I. As a species of the peptide, Applicants provisionally elect the peptide M6.1 having an amino acid sequence set forth in SEQ ID NO:191 (genus) and SEQ ID NO:375 (species). Claims 1, 2 and 6-15 read on peptide M6.1. In addition, the corresponding propeptide has the amino acid sequence set forth in SEQ ID NO:190. Claims 1 and 5 read on this propeptide. This election is made with traverse.

As is well known in the art, a particular class of conotoxins share a conserved cysteine framework, disulfide bridging pattern, conserved non-cysteine residues, and conserved molecular target. For example, it is known that  $\alpha$ -conotoxins, the conotoxins of the present invention, all share the following conserved four cysteine spacing (CC---C---C), with the first and third cysteines forming a disulfide bridge and the second and fourth cysteines forming a disulfide bridge. Additionally, almost all  $\alpha$ -conotoxins contain a conserved proline between the second and third cysteines. These conserved structural elements serve to form a very characteristic three dimensional structure for the  $\alpha$ -conotoxins (see the attached Figure 1). Note that the backbones of each  $\alpha$ -conotoxin shown in the attached Figure 1 are superimposable. Other than the conserved elements mentioned above, the sequences of the  $\alpha$ -conotoxins are quite divergent. Similarly, it is known that the  $\omega$ -conotoxins all share the conserved six cysteine spacing (--C---C---CC---C---C--).

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Additionally, the gene organization for all conotoxins has been characterized. As shown in Figure 2 attached hereto, each toxin is found at the C-terminal (3') end of the gene. There are two regions upstream of the toxin sequence in the gene. First, is a signal sequence used to target the protein into the appropriate cellular compartment in the venom-producing cells of the cone snails. This is followed by an intervening pro region whose function has not been determined. Analyses of sequences across all known conotoxin families have determined a very unexpected finding. All members of a conotoxin family share a conserved signal sequence that is different from that of even closely related families. For example, there are two families of conotoxins that share the same cysteine framework and disulfide bridging pattern (--C----C---CC---C----C--). They are the  $\omega$ -conotoxins and the  $\delta$ -conotoxins. However,  $\omega$ -conotoxins all inhibit subtypes of  $\text{Ca}^{+2}$  channels, while  $\delta$ -conotoxins all inhibit  $\text{Na}^{+}$  channel subtypes. Even though these two families share the same cysteine framework and disulfide bridging pattern, they have evolved to inhibit different molecular targets. It was found that the signal sequence of the  $\omega$ -conotoxins differs significantly from that of the  $\delta$ -conotoxins. Thus, the sequence of the signal sequence is predictive of a shared target in the nervous system.

The Examiner makes the claim that each sequence requires a separate search, in reasoning why the sequences were patentably distinct. Applicants assert that this is only a result of the limitations in programming of the search engines. There are chemical species of a core peptidic genus. Nothing prevents one skilled in the art from writing a program that would search the peptidic chemical genus as presently exists for the more traditional chemical genus. This lack of programming is due only to the way a skilled artisan would think about peptide chemicals (letter abbreviations, etc.).

Finally, the biological effects of  $\alpha$ -conotoxins appear to be diverse when delivered into model animals. It has been well established for EVERY  $\alpha$ -conotoxin investigated to date, however, that they all target nicotinic acetylcholine receptors with high affinity and selectivity. Thus, the conserved elements listed previously serve to confer a specific three-dimensional shape and a conserved function (the inhibition of nicotinic acetylcholine receptors). The conserved three dimensional structure of each conotoxin is equivalent to a conserved chemical core found in the

chemical genus often searched and patented by the PTO. The divergent sidechains amount to limited R-groups which are readily searched and allowed by the PTO. To make a distinction between a peptidic chemical genus is arbitrary and capricious.

The divergent biological effects observed for each  $\alpha$ -conotoxin are due to differences in function and localization for various nicotinic acetylcholine receptors targeted by the  $\alpha$ -conotoxins. Thus, the  $\alpha$ -conotoxins form a group of highly structurally and functionally related compounds. The same is true for other families of conotoxins that have been characterized ( $\delta$ -conotoxins target  $\text{Na}^+$  channels,  $\omega$ -conotoxins target  $\text{Ca}^{+2}$  channels, etc.) The Examiner's attention is further directed to McIntosh et al. (*Conus* Peptides as Probes for Ion Channels, Methods in Enzymology, Vol. 294, pp. 605-624, 1999), copy attached hereto, for a review of conotoxin families that goes into detail of the conservation within conotoxin families.

The subject application relates to  $\alpha$ -conotoxins which each have a conserved cysteine spacing, especially within each generic formula, a conserved disulfide bridging pattern, and a conserved molecular target. Thus, it is submitted that each sequence given in the claims represents a species of the  $\alpha$ -cono peptide genus, such as set forth in the generic formula of claim 1. Since all the species share a common structural motif and a common function, Applicants believe that restriction between the various species of this genus is unwarranted.

Furthermore, there are two criteria for a proper requirement for restriction between patentably distinct inventions: 1) The inventions must be independent or distinct as claimed; and 2) There must be a serious burden on the Examiner if restriction is not required. See MPEP § 803. Examiners must provide reasons and/or examples to support conclusions. For purposes of the initial requirement, a serious burden on the Examiner may be *prima facie* shown if the Examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant. Insofar as the criteria for restriction practice relating to Markush-type claims is concerned, the criteria are set forth in MPEP § 803.02. See MPEP § 803. If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the Examiner must

examine all claims on the merits, even though they are directed to independent and distinct inventions. In such a case, the Examiner will not require restriction. See MPEP § 803.02.

Applicants agree that the various conopeptides may be distinct from each other. However, as stated in the MPEP, as discussed above, distinctness alone is not enough to require a restriction. There must also be a serious burden upon the examiner. In the absence of such a burden, the examiner must examine all of the claims (or in this case, it is urged that all of the peptide claims should be examined). It is urged that the burden of examining all of the peptide claims of the present application is not a serious one, and that the burden of examining all of the peptide claims is only slightly greater than examining one of the groups of claims.

The examination entails various aspects. First is a decision concerning utility under 35 U.S.C. §101. Although each peptide species being claimed is distinct, they are all related in their structure and biological activity. Consequently, a decision concerning utility will be identical for all of the species, and there is no added burden of examining all of the species as compared to examining only a single species.

The second aspect of examination is whether the provisions of the various paragraphs of 35 U.S.C. § 112 have been met. In general, and in this case, this means reviewing the application and claims for compliance with the provisions of paragraphs 1 and 2 of § 112. As for the enablement aspect as found in paragraph 1 of § 112, all of the peptides are related in their structure and biological activity. Since no basis for distinguishing between the enablement of one species vs. another species has been set forth, it is presumed that all of the listed peptides will be treated equally. Again, this means that only a single decision needs to be made concerning all of the peptides. Therefore, this aspect of the examination will not be a serious burden if all peptides are examined, vs. only one of the peptides.

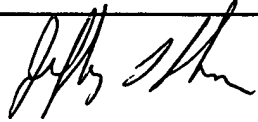
Concerning paragraph 2 of § 112, this involves the wording of the claims. The wording of the claims in each group of claims is identical except for the specified peptide. Consequently, any objections to the language of the claims for one Group of claims is equally applicable to the other Groups of claims. Therefore there is no increase in the burden concerning 35 U.S.C. § 112, second paragraph, if all peptide claims are examined.

The third aspect of examination is a review of prior art to determine whether the claims are anticipated or obvious. There are two aspects of such a search. A first aspect is a review of the prior art literature and patents. The literature to be reviewed will be identical for all of the peptides. All of the claimed peptides have similar, though not identical, structures and all are claimed to have the same utility. The Examiner has not stated that a search of the scientific literature will be any different for one peptide than for any other peptide. Consequently, the search of the patent literature will clearly be the same for all of the peptides. Because the search of the scientific literature and patent literature will be identical for all of the peptides, there is no added burden concerning this aspect if all of the peptides are examined. Furthermore, the search will probably entail a computer search based on the peptide sequences in the sequence listing. It is believed that such a search would identify prior art directed to the claimed peptides or peptides having the specified substitutions.

Consequently, it is submitted that the only reason for restriction is that the peptides are distinct from each other. But as explicitly stated in MPEP § 803, the inventions must be distinct and there must be a serious burden on the examiner. MPEP § 803.02 states that if a search and examination of an entire claim can be made without serious burden, the examiner must examine all claims on the merits, even though they are directed to independent and distinct inventions. As urged above, it is asserted that examination of all of the peptides claims will not impose a serious burden.

In addition, it is submitted that the computer search for the mature toxin will also identify and prior art disclosing the propeptide. Consequently no additional searching is required to examine the propeptides with the corresponding mature toxins, and thus no undue burden exists in this instance.

In view of the above arguments, it is requested that the restriction requirement imposed in the Office Action mailed 3 December 2002 be reconsidered and that all of the peptides be examined together.

RESPECTFULLY SUBMITTED,					
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